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BRIEF COMMUNICATION

Cognitive impairment in pulmonary arterial hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is characterized by progressive pulmonary vascular remodeling with resultant abnormal increase in pulmonary artery pressure and right heart dysfunction. There is evidence that PAH includes cognitive impairment. However, the cognitive impairment syndrome has not been well described, and both the underlying mechanism and the relationship between cardiopulmonary and cognitive dysfunction in PAH are unknown. We performed cognitive evaluations and same day sub-maximum cardiopulmonary exercise testing on adult subjects with PAH. A frontal–subcortical syndrome suggestive of vascular cognitive impairment was found in 26% of subjects and was associated with noninvasive markers of pulmonary vascular remodeling.

Introduction

Pulmonary arterial hypertension (PAH) is a complex disease characterized by progressive pulmonary vascular remodeling with resultant abnormal increase in pulmonary artery pressure and right heart dysfunction. Although PAH originates in the pulmonary vasculature, there is growing evidence that PAH represents a systemic disease with multi-organ involvement.[1] In fact, recent studies have suggested that cognitive impairment is present in nearly half of all PAH patients.[2,3] However, the underlying mechanism of cognitive impairment in PAH is uncertain and to date, there has been no association of aberrant cardiopulmonary parameters with cognitive impairment in PAH patients. We conducted a cross-sectional study to confirm the presence of cognitive impairment in PAH patients presenting to the Yale Pulmonary Vascular Disease (PVD) Clinic, examined its associations with markers of abnormal exercise cardiopulmonary measures, and delineated the characteristics of the cognitive impairment syndrome, with the goal of identifying potential underlying mechanisms.

Methods

We enrolled adult patients with an established diagnosis of PAH[4] from the Yale PVD clinic between 27 February 2020 and 9 December 2021. The study protocol was approved by the Yale University Institutional Review Board (IRB #2000027349) and all subjects provided written consent. Subjects underwent same day clinically indicated sub-maximum cardiopulmonary exercise testing (CPET). In our practice, sub-maximal CPET is performed at every out-patient clinic visit. Sub-maximum derived exercise variables have been shown to confer prognostic significance in pulmonary hypertension[5] and unlike conventional CPET, a maximum exercise effort is not required, making it an attractive option for patients with cardiopulmonary or musculoskeletal disorders and elderly patients who often are unable to undergo maximum exercise testing. The sub-maximum CPET involves subjects exercising by going up and down a step for 3 min while wearing a mouthpiece connected to a portable metabolic cart and a continuous gas exchange analyzer; a full protocol has been published previously.[6,7]

Subjects were assessed for cognitive impairment using the Self-Administered Gerocognitive Exam (SAGE), a screening tool that tests multiple cognitive domains and has been used to detect cognitive impairment in non-geriatric populations with systemic disease.[8] A score of <17 on the SAGE is consistent with cognitive impairment. Multivariable regression analysis was performed to assess relationships between SAGE scores and metrics of

cardiopulmonary function in PAH. All analysis was performed using Stata 17.

Results

Twenty-three subjects participated in the study (52% female, 91% Caucasian). Subject demographics are discussed in Table 1. No subjects carried a diagnosis of any cognitive impairment syndrome. Six out of 23 subjects (26%) met criteria for cognitive impairment (SAGE score <17), with SAGE scores ranging from 12 to 22. Most cognitively impaired subjects fell into the category of mild cognitive impairment (SAGE score 15–16).[9] All subjects who met criteria for cognitive impairment had difficulties on tests of executive functioning, and most had difficulty with memory, calculation, and visuospatial tests (Fig. 1). Exercise cardiopulmonary metrics utilized in the analysis include sub-maximum and extrapolated maximum exercise oxygen consumption (VO_2) (% predicted), ventilatory efficiency expressed as VE/VCO_2, oxygen uptake efficiency slope, gas exchange derived—pulmonary vascular capacitance (GX_{CAP}), rest and end exercise end-tidal carbon dioxide ($ETCO_2$), heart rate, and peripheral O_2 saturation. Extrapolated maximum VO_2 is obtained by mathematically extrapolating the relation between VO_2 and carbon dioxide production (VCO_2) to the point at which respiratory exchange has risen to double the value at the onset of exercise[10] or by using a logarithmic curve fitting model which incorporates the oxygen uptake efficiency slope.[11] Extrapolated maximum VO_2 has been shown to closely correlate with actual maximum VO_2 attained during exercise and is independent of exercise duration.[10,11] GX_{CAP} explained 29% of the variance in SAGE score, while systemic O_2 desaturation explained 20% of the variance, controlling for age and level of education (Table 2). There was no difference in SAGE score between subjects with and without right heart dysfunction.

Table 1. Subject demographics.

Participants (% female)	23 (52)
Average age in years (SD)	63 (13.1)
% Caucasian	91
% Hispanic	9
Average years of education (SD)	15.3 (2.38)
Etiology of PAH	
Idiopathic	12 (52%)
Connective tissue disease associated	9 (39%)
Pulmonary capillary hemangiomatosis	2 (9%)
NYHA class[a]	
I	6 (26%)
II	8 (35%)
III	8 (35%)
IV	0
Right heart enlargement (%)	14 (61)
Right heart dysfunction[b] (%)	10 (43)
Mean RVSP (SD)	57.16 (27.21)
Mean RAP (SD)	6.67 (1.15)
Mean RVEDP (SD)	11.75 (3.64)
Mean PAP (SD)	39.59 (13.02)
Mean PCWP (SD)	10.33 (4.04)
Mean PVR (SD)	5.89 (3.87)
SAGE scores	12–22
Cognitive impairment (%)	6 (26)

PAP, pulmonary artery pressure (mmHg); PCWP, pulmonary capillary wedge pressure (mmHg); PVR, pulmonary vascular resistance (wood units); RAP, right atrial pressure (mmHg); RVEDP, right ventricular end-diastolic pressure (mmHg); RVSP, right ventricular systolic pressure (mmHg).

[a]Percentages do not add up to 100% as one subject was missing NYHA classification.

[b]Defined as tricuspid annular plane systolic excursion ≤1.5 cm.

Discussion

Cognitive impairment was present in 26% of the patients in this study, with most of the cognitively impaired subjects falling into the category of mild cognitive impairment. This estimate of prevalence is lower than the 45%–58% cited in earlier studies[2,3]; this is possibly related to the fact that this study population appears to have less severe PAH according to the metrics in Table 1 than the populations used in prior studies. It is difficult to make comparisons between this study and previous work regarding severity of cognitive impairment as different scales of cognition and methods of analysis were used in all studies. However, a recent study involving patients with all types of pulmonary hypertension utilized similar methods to this one and reported that subjects with cognitive impairment scored predominantly in the mild cognitive impairment range.[12] The pattern of cognitive deficits shown by subjects in this study (Fig. 1), is similar to what has been reported previously. This constellation of impairment in which executive dysfunction is most commonly seen, followed by memory and visuospatial deficits, is consistent with a frontal-subcortical cognitive impairment syndrome.[13]

Frontal-subcortical cognitive impairment is most commonly associated with cerebrovascular disease.[14]

Cerebral vasomotor reactivity (VMR) reflects the compensatory constrictive or dilatory capacity of cerebral resistance vessels to a vasoactive stimulus.[15] There is a significant body of evidence linking impaired VMR with cerebrovascular cognitive impairment.[16–18] Reductions in VMR are well described in a variety of cardiovascular conditions including systemic hypertension and atherosclerosis.[19] Several studies have used noninvasive methods to suggest that there is decreased cerebral VMR

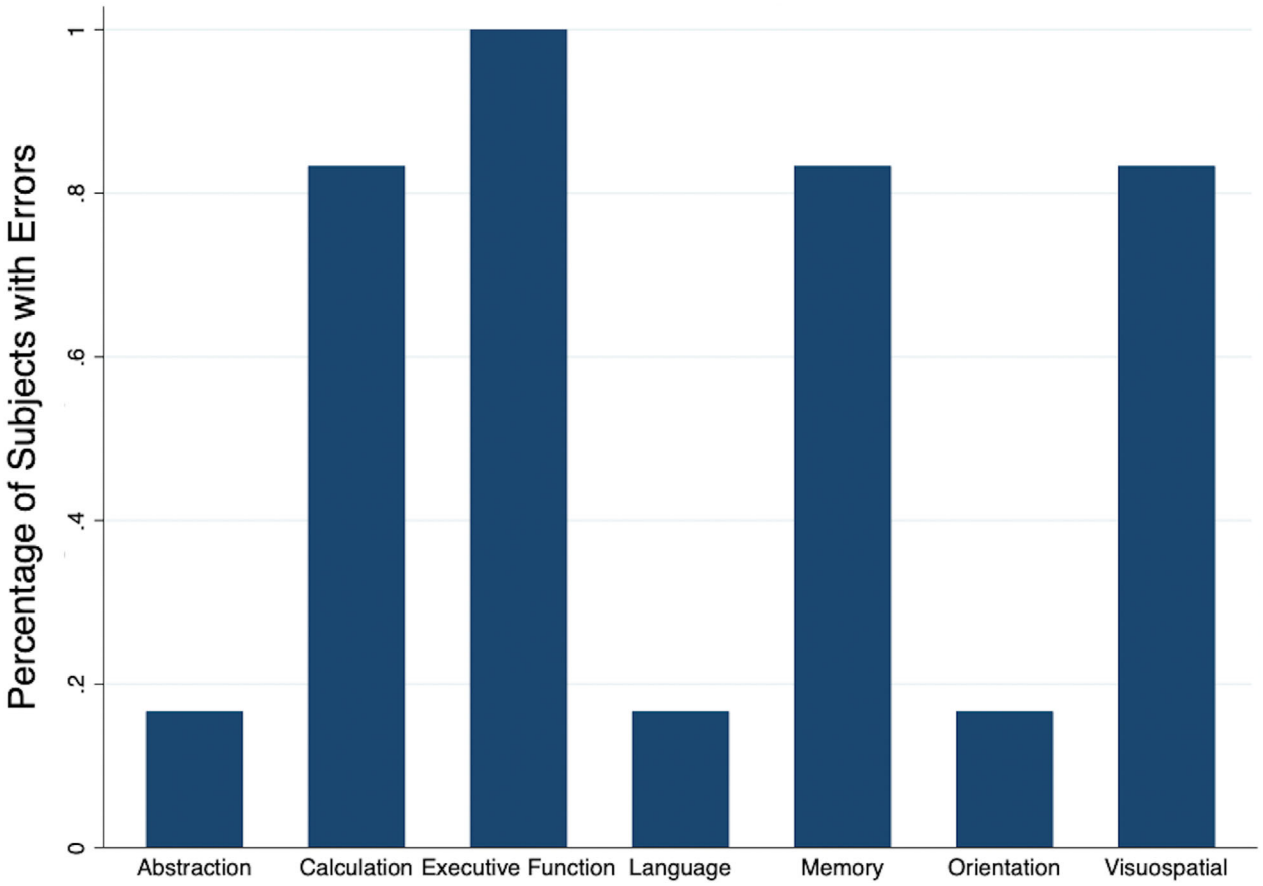

Figure 1. Characteristics of cognitive impairment in pulmonary arterial hypertension. All subjects with cognitive impairment demonstrated deficits in executive functioning, with most also demonstrating deficits on memory and visuospatial/calculation tasks. Orientation, abstraction, and language were relatively spared.

Table 2. Multivariable regression of SAGE score on pulmonary metrics of exercise tolerance, controlling for age, and level of education.

Metric	Adjusted R^2
$ETCO_2$ (%)[a]	0.12
SpO_2 (%)[a]	0.20
GX_{CAP}[b]	0.29
VE/VCO_2[c]	0.01
VO_2[d]	0.01
VO_2max[d]	0.05

[a]Change between rest and end exercise end-tidal carbon dioxide ($EtCO_2$) and peripheral oxygenation (SPO_2), expressed as percentage.
[b]Gas exchange derived—pulmonary vascular capacitance.
[c]Ventilatory efficiency.
[d]Sub-maximum (VO_2) and extrapolated maximum exercise oxygen consumption (VO_2max), (% predicted).

in PAH patients at rest, and both decreased cerebral blood flow and VMR in PAH patients during exercise.[20,21] However, the correlation between this and cognitive impairment in PAH patients is not known.

The metric most closely associated with cognitive impairment in this study was decreased GX_{CAP}, followed by systemic oxygen desaturation after exercise. We previously demonstrated that GX_{CAP} correlates with pulmonary artery compliance obtained during right heart catheterization.[6] Systemic oxygen desaturation in PAH is the result of reduced mixed venous oxygen saturation from diminished cardiac output or ventilation–perfusion mismatch from obliterative pulmonary vasculopathy. While dynamic opening of a patent foramen ovale (PFO) during exercise could also account for the systemic oxygen desaturation, this would simply reflect an increase in RV afterload or pulmonary vascular disease burden during exercise with resultant right to left shunt via the PFO. Hence, the decrease in GX_{CAP} and systemic O_2 desaturation observed in the current study most likely represent increased precapillary pulmonary vascular burden and vascular remodeling seen in PAH.[5]

The presence of a frontal-subcortical cognitive impairment syndrome that is most closely associated with

measures of increased pulmonary vascular remodeling suggests the possibility of cerebral vascular remodeling, causing impaired cerebral VMR and cognitive impairment. However, further investigation is needed to determine the relationship between cognitive impairment and pulmonary vascular and cerebrovascular remodeling in PAH. Decreased cerebral blood flow resulting from diminished cardiac output could play a role in this process as well; this study did not show any significant relationship between right heart function and cognitive impairment; however, no direct measures of cardiac output were used.

Limitations of this study include the small, majority Caucasian sample size and limited cognitive testing measures. However, PAH is a rare disease, which limits the accruement of potential subjects. We did not include a control group as this was a primarily descriptive study without an intervention. Although only a single cognitive test was used, this is a composite measure that contains the domains of interest, and allowed the enrollment of more subjects as it is self-administered. Additionally, the sub-maximum exercise protocol is not the gold standard for measuring cardiopulmonary deficits, which limits the ability to correlate exercise variables with cognitive impairment in this study. Directions for future studies include larger studies with more in-depth cognitive testing to confirm the frontal-subcortical syndrome and investigations of the relationship between pulmonary vascular remodeling, cerebrovascular disease, and cognitive impairment in PAH using invasive CPET.

Author Contributions

SH: design of study, acquisition and analysis of data, manuscript drafting. CS: acquisition of data, manuscript drafting. IS: design of study, acquisition and analysis of data, manuscript drafting. CF: manuscript drafting.

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Conflict of Interest

No authors have any potential conflicts of interests to disclose.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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